REMARKS

With entry of this Amendment, claims 1, 2, 5-16, 18–46, and 56-70 are pending in this application. Claims 56-70 have been added. Claim 56 is directed toward a composition prepared according to the method of claim 10 and is supported, for example, in the examples. Claim 57 is previously cancelled claim 4. Claim 58 encompasses a particular embodiment of claim 1 and is supported, for example, by the specification on page 4, paragraph 12. Claims 59-61 are drawn to methods using particular bases previously recited in method claim 10. Claim 62 recites the product of claim 1 prepared by the process described in Claim 10. Claim 63 depends from claim 62 but recites a different range of anti-Xa activity. Claim 64 recites the composition of claim 1, further reciting a phosphazene base used in at least one example. Claim 65 recites the product of claim 1 reciting another phosphazene base used in at least one example. Claims 66-69 recite embodiments of the invention wherein the base is defined as having a pKa greater than 20. The subject matter of claim 70 is reasonably conveyed by the specifically disclosed base 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diaza-phosphorine. Each of the new claims is supported by the specification as originally filed. New claims 56-70, as well as the amendment to existing claims, add no new matter.

The Claims Are Enabled

The Examiner rejects claims 10-16, and 18-37 under 35 U.S.C. § 112, first paragraph. *See* Office Action at 2. According to the Examiner, the specification does not enable one skilled in the art to prepare "more than two alkali or alkaline-earth metal salt[s] of more than two sulfated polysaccharide[s] of heparin and treatment of

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thrombotic accidents."[1] *Id.* To reach this conclusion, the Examiner considers some, but not all, of the factors set out in *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988). *See id.* at 3-5.

Applicants respectfully traverse. First, the Examiner has provided no evidence or reasoning as to why methods of the present invention do not enable one of skill in the art to prepare multiple alkali and alkaline earth metal salts. The specification describes compositions comprising alkali and alkaline-earth metal salts such as sodium, potassium, calcium, and magnesium made by the method disclosed. *See* ¶ 17.

Second, the examiner has provided no evidence or reasoning as to why the methods of the present invention do not enable one of skill in the art to prepare multiple sulfated polysaccharides of heparin. The compositions produced by the claimed method are mixtures of polysaccharides comprising varying saccharide unit lengths. It is well-recognized in the art that low molecular weight heparin polysaccharides comprise fragments of varying lengths, i.e., multiple sulfated polysaccharides of heparin. For example, Mardiguian (U.S. Patent No. 6,384,021) describes the heparin fragments produced by the chemical methods known in the art as a mixture of fragments (Col. 1, ll. 31-35) and describes his own composition as containing heparin fragments of varying lengths (e.g., Col. 2, ll. 23-29).

The Examiner has provided no explanation of why one skilled in the art would be forced to engage in undue experimentation in order to perform the disclosed steps in

[1] Applicants respectfully note that none of claims 10-16 and 18-37 recites methods for treating thrombotic accidents. Moreover, as the Examiner acknowledges on page 2 of the Office Action, the claims recite "at least one" salt and "at least one" polysaccharide, not more than two salts or polysaccharides.

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the presence of multiple alkali or alkaline earth metal salts and thereby make more than one salt of heparin of more than one sulfated polysaccharide of heparin. The *Wands* factors considered by the Examiner do not support his conclusion. For example, the Examiner first states that "[t]he scope of the claims is seen to include the method of preparing two or more alkali or alkaline earth metal salts of two or more sulfated polysaccharide[s] of heparin." Office Action at 3. In fact, there are only 10 possible non-radioactive alkali and alkaline earth metals. Further, as explained above, methods for preparing the two or more sulfated polysaccharides of heparin are known in the art.

The Examiner next contends that the prior art fails to disclose "methods of preparing two or more alkali or alkaline earth metal salts of two or more sulfated polysaccharide[s] of heparin." Office Action at 3-4. Again, however, the Examiner fails to provide reasoning or evidence of nonenablement, and Mardiguian reports that prior art compositions and his own compositions contain multiple sulfated polysaccharides of heparin. *See* Col. 1, ll. 31-35; Col. 2, ll. 23-29. And, for the reasons above, preparing two or more salts of those polysaccharides is a matter of routine skill, not undue experimentation.

Third, the Examiner asserts that "there is not seen to be sufficient data to substantiate that two or more alkali or alkaline earth metal salts of two or more sulfated polysaccharide[s] of heparin could be made." But, the Examiner has not established a *prima facie* need for data: "[i]f one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art." M.P.E.P. § 2164.03. Here, the Examiner has provided no evidence or reasoning as to why one skilled in the art would have difficulty carrying out

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or predicting, the use of more than one alkali or alkaline earth metal salt to prepare a composition that would comprise two or more alkali or alkaline earth metal salts of tow or more sulfated polysaccharides of heparin.

Fourth, the Examiner contends that the specification provides insufficient guidance to permit the skilled artisan to extrapolate from the exemplified sodium salts of sulfated polysaccharides of heparin to the two or more alkali or alkaline earth metal salts encompassed by the claims. *See* Office Action at 4. As explained above, however, the Examiner has provided no evidence or reasoning as to why one skilled in the art would not readily understand that if more than one alkali or alkaline earth metal salt was used in the claimed methods, two or more alkali or alkaline earth metal salts of two or more sulfated polysaccharides of heparin would result. Here, a single embodiment, a sodium salt of sulfated polysaccharides of heparin, provides broad enablement where the Examiner has provided no evidence or reasoning that the result of including multiple alkali or alkaline earth metal salts in the claimed methods would not be routine or predictable. *See* M.P.E.P. § 2164.03.

Finally, the Examiner asserts that the examples are drawn to methods of preparing a single salt of a single sulfated polysaccharide of heparin and that undue experimentation would be necessary to go beyond the examples. *See* Office Action at 5. As explained above, however, it is known in the art that preparations of low molecular weight heparin can comprise multiple sulfated polysaccharides of heparin. Moreover, the Examiner has provided no reasoning or evidence that it would not be well within the skill in the art to include multiple alkali or alkaline earth metal salts in the claimed methods to produce more than one alkali or alkaline earth metal salt.

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In conclusion, the Examiner has failed to establish a *prima facie* case that the preparation of multiple alkali or alkaline earth salts of multiple sulfated polysaccharides of heparin is not a matter of routine skill given the disclosure of the present invention. Applicants respectfully request the reconsideration and withdrawal of the rejection of claims 10-16, and 18-37, as amended, under 35 U.S.C. § 112, first paragraph.

The Claims Are Definite

The Examiner rejects claims 39-46 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for their recitation of "'the source of an active agent' [which] does not result in a patentably distinguishable methodological and manipulative difference in how said active agent's source impacts the method from which it depends ...." Office Action at 6.

Applicants respectfully traverse this rejection because the active agent prepared by the claimed methods is patentably distinguishable (see below). Solely to expedite prosecution, however, claims 39-46 have been amended to depend from composition claims 1-2 and 57. These amendments do not narrow the scope of the amended claims; rather, they broadly recite compositions that are not limited to methods of preparation.

Additionally, the Examiner rejects claims 39-46 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for their recitation of "thrombotic accidents." Though the term accident is used in the original disclosure and is a term with a common meaning, such as "events," Applicants have amended the claims to recite arterial thrombosis, thereby obviating this rejection. These amendments do not narrow these claims, in fact, they broaden the scope of the claims to recite arterial thrombosis

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generally, which is reasonably conveyed by the specification. In light of these amendments, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of claims 39-46, as amended, under 35 U.S.C. § 112, second paragraph.

The Claims Are Not Anticipated Or Rendered Obvious by Mardiguian

The Examiner rejects claims 1-3, and 5-9 under 35 U.S.C. § 102(e) as allegedly anticipated by Mardiguian.[2] Specifically, according to the Examiner, U.S. Patent No. 6,384,021 discloses compositions comprising sulfated polysaccharides of heparin with an anti-Xa activity in the range of 100-150 IU/mg, an anti-IIa activity less than or equal to 10 IU/mg, containing 10-12 saccharide units and a 4,5-unsaturated glucuronic acid-2-O-sulphate unit, with an anti Xa:anti-IIa ratio greater than 10, and a sodium salt. Office Action at 7.

Applicants respectfully traverse. "A claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently in a single prior art reference." *Verdegaal Bros v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987); *see also* M.P.E.P. § 2131. Because Mardiguian does not disclose all of the elements of claims 1 and 2 (and claims 5-9, which depend therefrom), Mardiguian cannot anticipate those claims.

Claim 1 recites a composition defined, *inter alia*, as having a mean molecular weight of 1500 to 3000 Daltons, an anti-Xa activity in the range of 110 to 150 IU/mg, an anti-IIa activity up to 10 IU/mg, and an anti-Xa:anti-IIa ratio greater than 10. Claim 2

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[2] Cancellation of claim 3 renders its rejection moot.

recites a composition defined, *inter alia*, as having a mean molecular weight of 1500 to 3000 Daltons and an anti-Xa activity in the range of 110 to 150 IU/mg. In contrast, although Mardiguian generally discloses compositions having an average molecular weight range of 2000-4000 Daltons (Col. 2, ll. 23-25), Mardiguian does not disclose compositions of 3000 Daltons or less having an anti-Xa activity in the range of 110-150 IU/mg, as recited in the claims.

Rather, as seen in the table in Column 5 of Mardiguian, the method disclosed in that patent teaches that a composition with an anti-Xa activity of 110 or greater occurs only if the molecular weight is significantly above 3000. In fact, the patent teaches that as the anti-Xa activity increases, the molecular weight also increases (see summary of examples 1-5, Col. 5). One can see this from example 2 in the table where an anti-Xa of 110 requires a molecular weight of 3616 and example 1 where an activity of 120 requires a molecular weight of 3650.

Hence, not only does Mardiguian not anticipate the claims, Mardiguian would lead one skilled in the art to predict that preparations of low molecular weight heparin with anti-Xa activity greater than 110 IU/mg would have molecular weights greater than 3600 Daltons. Mardiguian thus teaches away from the invention recited in claim 1, wherein the mean molecular weight does not exceed 3000, even when the anti-Xa activity reaches 150 IU/mg. Because the reference relied on by the Examiner neither teaches nor suggests the compositions of the present invention, Applicants respectfully request the withdrawal of the rejection of claims 1, 2, and 5-9 under 35 U.S.C. § 102(e).

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CONCLUSION

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated by nor obvious in view of the cited prior art. Nor are the claims non-enabled or indefinite. Applicants respectfully request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 14, 2004

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